PATENT

Attorney Docket No. 11160-002

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Inventor:	Kivlighn et al.	)
		) Group Art Unit: 1617
Serial No.:	09/892,505	)
		) Examiner: Kantamneni, Shobha
Filed:	June 28, 2001	)

Title: Treatment For Cardiovascular Disease

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Sir:

APPELLANT'S BRIEF UNDER 37 CFR 41.37

This brief is in furtherance of the Notice of Appeal filed in this application on June 9, 2008. A Fee Transmittal form PTO/SB/17 is transmitted concurrently with this paper to authorize the payment of the fee required for submittal of this brief.

1. REAL PARTY IN INTEREST - 37 CFR 41.37(c)(1)(i)

The real party in interest in this Appeal are the assignees University of Washington, Seattle, WA and Merck & Co., Inc., Rahway, NJ.

2. RELATED APPEALS AND INTERFERENCES - 37 CFR 41.37(c)(1)(ii)

There is no other appeal, interference or judicial proceeding that is related to or that will directly affect, or that will be directly affected by, or that will have a bearing on the Board's decision in this Appeal.

3. STATUS OF CLAIMS - 37 CFR 41.37(c)(1)(iii)

Claims pending: 16-18

Claims cancelled: 1-15

Claims withdrawn but not cancelled: none

Claims allowed: none

Claims objected to: none

Claims rejected: 16-18

The claims on appeal are 16-18.

4. STATUS OF AMENDMENTS - 37 CFR 41.37(c)(1)(iv)

A non-final office action issued on February 7, 2008. Amendments submitted prior to this non-final office action were previously entered. Appellant/Applicant appeals the rejections of claims set for in the February 7, 2008 office action.

5. SUMMARY OF THE CLAIMED SUBJECT MATTER- 37 CFR 41.37(c)(1)(v)

This invention relates generally to a method of treating hypertension.

With reference to paragraphs, pages, line numbers, figures and item numbers as provided in the specification, independent claim 16 is directed to a method of reducing uric acid in a patient in need thereof to treat a condition (page 8, lines 30-32, page 11, lines 20-30), said method comprising

administering to said patient a therapeutically effective amount of a composition comprising a xanthine oxidase inhibitor, or a pharmaceutically acceptable salt thereof (page 12, lines 7-17) to achieve a uric acid level in the patient of 4-6 mg/dl (page 11, lines 20-30), wherein said condition is hypertension (page 8, lines 30-32; page 11, lines 20-30).

With reference to paragraphs, pages, line numbers, figures and item numbers as provided in the substitute specification, independent claim 17 is directed to a method of reducing uric acid in a patient in need thereof to treat a condition (page 8, lines 30-32, page 11, lines 20-30), said method comprising

administering to said patient a therapeutically effective amount of a composition comprising allopurinol, or a pharmaceutically acceptable salt thereof (page 12, lines 7-17) to achieve a uric acid level in the patient of 4-6 mg/dl (page 11, lines 20-30), wherein said condition is hypertension (page 8, lines 30-32; page 11, lines 20-30).

With reference to paragraphs, pages, line numbers, figures and item numbers as provided in the substitute specification, independent claim 18 is directed to a method of treating hypertension (page 8, lines 30-32, page 11, lines 20-30) in a subject in need, said method comprising

administering to said patient a therapeutically effective amount of a composition comprising allopurinol, or a pharmaceutically acceptable salt thereof (page 12, lines 7-17).

6. GROUNDS OF REJECTION TO BE REVIEWED UPON APPEAL - 37 CFR 41.37(c)(1)(vi)

a. The grounds for rejection for claims 16-17 is that each claim is obvious under 35 USC § 103(a) by the Maeda et al. reference (U.S. Pat. No. 5,747,495) in view of the Nakamoto et al. reference (EP 0337350), and further in view of applicant's admission.

b. The grounds for rejection for claim 18 is that it is obvious under 35 USC § 103(a) by the Baldwin et al. reference (U.S. Pat. No. 4,058,614) in view of the Baldwin et al. reference (U.S. Pat. No. 4,032,522).

7. ARGUMENT 37 CFR 41.37(c)(1)(vii)

a. Rejection of claims 16-17: The Maeda et al. reference either alone or in combination with the Nakamoto et al. reference does not render claims 16-17 as obvious.

Applicants will set forth below their primary point of argument, supported by Expert Declarations from independent experts in the field of hypertension, as to why the Maeda et al. reference and the Nakamoto et al. references do not render claims 16-17 obvious: the Maeda et al. reference and the Nakamoto et al. reference, either alone or in combination, do not reasonably establish a reasonable expectation of success of treating hypertension by controlling uric acid. All claims rise and fall together for this rejection.

The Maeda et al. reference discloses that 4-amino-6-hydroxypyrazolo [3,4-d]pyrimidine (AHPP) serves as an inhibitor against xanthine oxidase, and that AHPP can reduce blood pressure by enhancing endothelium derived relaxing factor (EDRF) "due to a decrease in superoxide or radical generation, more specifically by a novel mode between action by inhibiting the interaction of EDRF (which is now identified as nitric oxide) and superoxide (O_2^-). The Maeda et al. reference also disclosed that AHPP could transiently lower blood pressure in the Spontaneous Hypertensive Rat (SHR). See Col. 5 line 53 to Col 6., line 30 of Maeda et al. reference. However, other than using uric acid as a marker to determine whether the AHPP inhibited xanthine oxidase *in vitro*, nowhere does the Maeda et al. reference hint that uric acid levels should be targeted as a means to lower blood pressure. The Examiner nearly acknowledges this as evidenced by her statement that "Maeda et al. do not explicity teach the administration of a therapeutically effective amount of xanthine oxidase inhbitor to achieve a uric acid level in the patient of 4 to 6 mg/dl in treating hypertension. Maeda et al. do not teach administration of a therapeutically effective amount of allopurinol to achieve a uric acid level in the patient of 4 to 6 mg/dl in treating hypertension" (Page 3, 2nd and 3rd paragraphs of February 7, 2008 office action). In reality, nowhere in the Maeda et al. reference can it be reasonably said that Maeda et al. suggests that uric acid causes hypertension and that controlling uric acid serves to treat hypertension.

As further support to this point, Applicants submitted on October 31, 2007 a Declaration from Dr. Rodriguez-Iturbe, President-Elect for the International Society of Nephrology (Evidence Appendix Exhibit A). Dr. Rodriguez-Iturbe has conducted extensive studies in the

SHR rat and is a world expert in the field of high blood pressure and nephrology. Dr. Rodriquez-Iturbe states the following in his declaration:

> Much of my research has focused on animal models of hypertension, including studies in the SHR rat[1-4]. This is a hereditary model of hypertension that we and others have shown is mediated by oxidative stress. While I am aware that xanthine oxidase inhibitors have been reported to lower blood pressure transiently in this model[5] (also the Maeda Patent U.S. Patent 5,747,495), none of those studies suggested that this was due to uric acid, but rather asserted that this was due to oxidative stress. In fact, uric acid is considered an antioxidant and in some recent pilot studies we can show that it can lower blood pressure in these animals. Furthermore, most of the studies documenting oxidative stress in models of hypertension have focused on the role of NADPH oxidase, either produced by vascular cells[6,7] or by the inflammatory cells themselves[1-4]. (emphasis added)

Dr. Rodriguez-Iturbe clarifies that Maeda et al. does not suggest that the transient lowering of blood pressure by AHPP is due to uric acid, but rather was due to oxidative stress. Dr. Rodriguez-Iturbe also points out that uric acid is considered an antioxidant and states that uric acid can even lower blood pressure in the SHR rat. This evidence certainly argues against lowering uric acid, and at a minimum, invalidates the interpretation of Maeda et al.'s SHR data as leading one to target uric acid to predefined levels.

More to the issue of the lack of expectation of success by those in the art, Dr. Rodriguez-Iturbe makes clear that the studies in the SHR rat, such as those presented in the Maeda patent, ultimately lead those skilled in the art away from using xanthine oxidase inhibitors as a treatment for hypertension, and certainly did not suggest targeting uric acid to predetermined levels. Particularly relevant to this point, Dr. Rodriguez-Iturbe states the following:

> I therefore conclude that the concept of lowering uric acid as a means to control blood pressure was a novel idea for which Dr Johnson brought forth the first direct experimental[8] as well as human[12] evidence. Studies in the SHR rat did not provide a reasonable expectation to those skilled in the art of successfully treating

> hypertension via administration of x.o. inhibitor, much less did they teach or suggest to those skilled in the art to use x.o. inhibitors as a means to lower blood pressure by reducing uric acid levels. Paragraph 3, Rodriguez-Iturbe Declaration (emphasis added).

Dr. Rodriquez-Iturbe's statement above concerning the lack of any reasonable expectation of success is corroborated by Dr. George Bakris as evidenced in the DECLARATION OF GEORGE BAKRIS, M.D. submitted to the USPTO on October 31, 2007 (Evidence Appendix, Exhibit B). Dr. Bakris is a Professor of Medicine and is the Director of the Hypertensive Diseases Center at the University of Chicago, Pritzker School of Medicine. Dr. Bakris is a recognized world expert in the field of high blood pressure is also a member and coauthor of the Joint National Committee 7 on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, which provides the primary guidelines for blood pressure management in the United States. With respect to hypertension studies in the SHR, Dr. Bakris states the following:

> I am aware that there were earlier studies in which it was reported that xanthine oxidase inhibitors could lower blood pressure in the spontaneously hypertensive rat (SHR)[4]. The authors of the SHR studies always thought that the xanthine oxidase inhibitors were functioning as antioxidants since they block xanthine oxidase-generated oxidants. In particular, never was efficacy linked with targeting uric acid levels to certain ranges. Moreover, the concept that these agents might be useful to treat hypertension was thwarted by the fact that these inhibitors did not lower BP in longterm studies in the SHR[5-7]. (emphasis added)

The declarative statements by two experts in the field of hypertension substantiate that there simply was no reasonable expectation in the art that lowering uric acid levels would be thought to be effective in treating hypertension. The following statement by Dr. Bakris probably encapsulates this conclusion best: prior to Dr. Johnson's work "[T]he longstanding belief, based on studies such as the Framingham Heart Study[3], was that elevated uric acid in hypertension was a secondary phenomenon and not causative of hypertension. Moreover, the notion of prescribing

medicines to lower uric acid for treating hypertension would have been considered, by experts in the field, as an improper and wasteful medical practice. As such, we did not list uric acid as a risk factor for hypertension in the JNC7 report, nor was this done by any other major society." (emphasis added).

Dr. Bakris expert statements in conjunction with Dr. Rodriguez-Iturbe's statements, and their cited references make abundantly clear that those skilled in the art would not have expected that hypertension could be treated by targeting uric acid. As further corroborative evidence of this, Applicants cite to the famous Framingham Heart Study (Culleton *et al*., *Ann Intern Med*, 131:7-13 (1999) submitted in the evidence appendix):

> "[O]ur findings from a community-based prospective study of 6763 adult men and women suggest that an elevated serum uric acid level is not causally associated with increased risk for coronary heart disease, death from cardiovascular disease, or death from all causes. …From a clinical perspective, serum uric acid level should not be used as an indicator of risk for cardiovascular disease; established risk factors should be used to stratify risk." (emphasis added).

Thus, Applicant has provided expert evidence and related prior art references which establish that no expectation of successfully treating hypertension by lowering uric acid existed at the time of filing the present application. The Examiner has not properly considered such evidence nor proffered any evidence refuting the conclusions made in the evidence provided by the Applicants. Expert evidence of nonobviousness may include evidence of the state of the art, the level of skill in the art, and the beliefs of those skilled in the art. See, e.g., *In re Oelrich,* 579 F.2d 86, 91-92, 198 USPQ 210, 214 (CCPA 1978) (Expert opinions regarding the level of skill in the art were probative of the Nonobviousness of the claimed invention.)*In re Beattie*, 974 F.2d 1309, 1313, 24 USPQ2d 1040, 1042-43 (Fed. Cir. 1992) (Office personnel should consider declarations from those skilled in the art praising the claimed invention and opining that the art teaches away from the invention.)Applicants reiterate that the Maeda et al. reference cited by the Examiner does not teach targeting of uric acid to treat hypertension, much less specified levels of uric acid, and this is acknowledged by the Examiner. In an effort to cure this acknowledged deficiency of the Maeda et al. reference, the Examiner cited to the Nakamoto et al. reference.

The Nakamoto et al. reference discloses a new uricosuric agent, as opposed to a xanthine oxidase inhibitor for the purpose of treating hyperuricemia (gout). Thus, the Nakamoto et al. reference relates to an entirely different type of compound. However, the Nakamoto et al. reference makes a curious statement, which the Examiner relies on for her allegation that Nakamoto discloses that compounds which reduce uric acid are effective in curing hypertension. The Nakamoto patent states that its diuretic compound, as opposed to a xanthine oxidase inhibitor, "is effective in curing gout by ameliorating and curing hyperuricemia. This disease often accompanies hypertension, arteriosclerosis and myocardial infarction because of characteristics of the disease. Accordingly, the compound of the present invention is effective in curing or preventing hypertension, arteriosclerosis or myocardial infarction accompanied by hyperuricemia." (page 7, lines 55-59 of Nakamoto et al. reference). The Examiner relies on this statement to theorize that it would have been obvious to target uric acid to treat hypertension in view of the Nakamoto et al. reference, and that one skilled in the art would have discovered through routine optimization those specific uric acid levels to achieve the desired effect of treating hypertension. Applicants will explain below how the Nakamoto statement is so flawed from a scientific perspective that those skilled in the art would not interpret it to teach the treatment of hypertension by targeting uric acid to predetermined levels. Moreover, Applicants point out that this single unsupported statement can not legitimately be said to somehow supplant the surplus of literature, scientific studies, and expert opinion concerning how uric acid was believed to have no causal connection to hypertension.

The Applicants submitted the SECOND DECLARATION OF RICHARD JOHNSON, M.D. on October 31, 2007 (Evidence Appendix, Exhibit C) and the DECLARATION OF MATTHEW R WEIR, M.D. on December 10, 2007 (Evidence Appendix, Exhibit D), which addressed the Nakamoto et al. reference, and in particular the statement the Examiner relies on for notion that Nakamoto et al. teach treating hypertension by lowering uric acid. Dr. Weir is the Director of the Division of Nephrology at the University of Maryland School of Medicine and a world expert in the field of hypertension. The declarations of Drs. Johnson and Weir prove that the statement made in the Nakamoto patent relied on by the Examiner is so flawed that it would not be given any weight, and indeed was not given weight by those skilled in the art. In particular, Dr. Weir states the following:

> Nakamoto reasons that if gout is associated with hypertension, then curing gout with its uricosuric compound will cure hypertension (page 7, lines 55-59). In fact, it has been known for over 40 years that uric acid is strongly associated with hypertension[2]. Nevertheless, those skilled in the art of science and medicine are careful to not confuse something considered as an associative factor with something that is a causative factor. Nakamoto made the classic mistake of equating association with causation. As an example, let's assume that a study finds that drinking alcohol is associated with lung cancer. Those skilled in the art would not assume from this that drinking alcohol causes lung cancer (rather the medical community would undoubtedly interpret this study to mean that many people who drink also smoke). The only way to determine whether abstaining from alcohol causes lung cancer or to determine whether uric acid causes hypertension is to test the hypothesis by conducting a scientific study.

The above quote from Dr. Weir shows how those skilled in the art would interpret the statement made in the Nakamoto patent that is relied on by the Examiner. This statement would be discounted outright and would not represent any credible teaching to those skilled in the art concerning whether uric acid should be targeted to control hypertension. In fact, the evidence surrounding the Nakamoto patent reveals that the Nakamoto patent was never accepted by those skilled in the art as teaching a treatment of hypertension. Dr. Weir goes on to explain:

> While the association of uric acid with hypertension has been known since our early work, this certainly did not prove that uric acid is a cause of hypertension. Indeed, the scientific community (as exemplified by guidelines published by the major societies on hypertension and cardiovascular disease) have not considered uric acid as having a causal role in hypertension. In this regard, Dr Johnson is the first to specifically investigate if uric acid might be a cause of hypertension and to provide direct evidence of such. As such, the Nakamoto reference is flawed from a medical/scientific perspective that even a person with little skill in the art would discount it outright, especially since Nakamoto provides zero supporting data or evidence that uric acid is a cause of hypertension. Consistent with this point, a

> literature search in the PubMed and patent search of the USPTO database using the authors' names (and U.S. Counterpart 4,883,821) identified no citations to their work. (emphasis added).

Ultimately, the single, unsupported statement in the Nakamoto et al. reference does not counter the overwhelming evidence provided by the Applicants establishing that those skilled in the art would not have reasonably expected that hypertension could be treated by targeting uric acid to specified levels. The following statement by Dr. Weir summarizes this best:

> "Members of the famous Framingham Heart Study group, experts in the field of hypertension, declared in 1999 (note the Nakamoto patent was issued in 1991) that uric acid does not play a causative role in hypertension[3], such conclusion being supported by a comprehensive scientific study. Indeed, as of 2000, the scientific evidence supported by actual research and data, lead those skilled in the art to believe that there is no reasonable expectation of successfully controlling hypertension by controlling a patient's uric acid levels. Said differently, the scientific, peer-reviewed literature taught away from controlling uric acid levels to control hypertension. Incidentally, in 2005, members of the Framingham Heart Study Group reversed their position and published an acknowledgement that serum uric acid plays a causative role in hypertension[4], citing to Dr. Johnson's work[5] . (emphasis added)

In order for an Examiner to successfully establish a *prima facie* case of obviousness based on a combination of references she must show (1) a finding that there was some teaching, suggestion, or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; and (2) a finding that there was reasonable expectation of success. M.P.E.P. § 2143. Furthermore, where the teachings of the prior conflict, the Examiner must weigh the suggestive power of each reference. M.P.E.P. § 2143.01. The Applicants have provided Expert Declarations from four world renown experts in the field of hypertension, coupled with related prior art references dated just prior to the filing of the present invention, which strongly establish

that no reasonable expectation existed to treat hypertension by controlling uric acid, much less targeting specific uric acid levels. No evidence has been proffered by the Examiner that refutes the expert declarations provided by Applicants. Essentially, in view of the Examiner's acknowledgement that the Maeda et al. reference does not teach treating hypertension by controlling uric acid, the Examiner's case for obviousness boils down to the single, confusing, clearly erroneous, and unsupported statement in the Nakamoto et al. reference. Applicants assert that a careful and fair review of the all of the evidence clearly reveals that no reasonable expectation of successfully treating hypertension by administering a xanthine oxidase inhibitor to lower uric acid levels to 4-6 mg/dl existed. Applicants respectfully request this rejection of claims 16 and 17 be withdrawn.

b. Rejection of claim 18: The Baldwin et al. reference does not render claim 18 obvious

Applicants will provide below their two primary points of argument as to why the Baldwin et al. reference does not render claim 18 obvious: (1) There is no suggestion found in the Baldwin et al. reference or in the cited art to modify the Baldwin et al. reference to achieve the invention defined in claim 18, and (2) there is no reasonable expectation found in the prior art of successfully treating hypertension by administering allopurinol.

The Baldwin et al. reference describes a new class of substituted imidazole compounds and teaches that certain imidazole compounds are useful as xanthine oxidase inhibitors whereas others are useful as anti-hypertensive agents. As an initial matter, Applicants assert that it is not clear that Baldwin even teaches that any of the imidazole compounds have both anti-uricemic and hypotensive properties. Baldwin stresses that certain compounds of the class are useful as either an anti-hypertensive agent **or** as a xanthine oxidase inhibitor. See Col. 2, lines 14-19. These statements strongly suggest that Baldwin does not connect the inhibition of xanthine oxidase with the lowering of blood pressure, and in fact suggests that the inhibition of xanthine oxidase and the lowering of blood pressure involved different imidazole compounds. Furthermore, Baldwin does not reference allopurinol which is a xanthine oxidase inhibitor and not an imidazole, nor does he relate the lowering of blood pressure with a target uric acid level. It must be acknowledged that it is unfair to make the logical leap that just because certain imidazole derivatives can be used as anti-hypertensive agents, that allopurinol, an entirely different class of compound that happens to be a xanthine oxidase inhibitor, can be used to treat

hypertension. Indeed, the fact that only a few of the possible imidazole compounds taught in the Baldwin et al. reference have hypotensive properties demonstrates that there can be no suggestion that any compound of the imidazole derivatives can be used to treat hypertension, much less an entirely different class of compound such as allopurinol. The finding that certain imidazole derivatives may have hypotensive properties does not provide a legitimate basis for modifying the Baldwin et al. reference for the notion that allopurinol will also lower hypertension. This is especially true in view of the expert evidence provided by Applicants that states that, at the time of filing the present application, there was no reasonable expectation of successfully treating hypertension by administering allopurinol.

A *prima facie* case of obviousness requires that the Examiner find that there was a suggestion to combine or modify the cited reference(s) and that there must be a reasonable expectation of success. Applicants assert that neither of these findings can be established. There is no suggestion to modify the Baldwin et al. reference to somehow concoct a method of treating hypertension by administering allopurinol. Furthermore, substantial evidence provided by the Applicants establishes that even if such modification to the Baldwin et al. reference were made, there would have been no reasonable expectation of successfully treat hypertension by administering allopurinol. In view of the foregoing arguments, Applicants respectfully request that the 35 USC 103(a) rejection of claim 18 be withdrawn.

8. CLAIMS APPENDIX - 37 CFR 41.37(c) (1) (viii).

A copy of the claims involved in this appeal is attached as a claims appendix under 37 CFR 41.37(c) (1) (viii).

9. EVIDENCE APPENDIX - 37 CFR 41.37(c) (1) (ix)

Copies of evidence involved in the appeal and submitted to the Examiner under 37 CFR 41.37(c) (1) (ix)is attached as evidence appendix under 37 CFR 41.37(c) (1) (ix).

10. RELATED PROCEEDINGS APPENDIX - 37 CFR 41.37(c) (1) (x)

None is required under 37 CFR 41.37(c) (1) (x).

Respectfully submitted,

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APPENDIX OF CLAIMS ON APPEAL

16 (previously presented) A method of reducing uric acid in a patient in need thereof to treat a condition, said method comprising administering to said patient a therapeutically effective amount of a composition comprising a xanthine oxidase inhibitor, or a pharmaceutically acceptable salt thereof, to achieve a uric acid level in the patient of 4 to 6 mg/dl, wherein said condition is hypertension.

17. (previously presented) A method of reducing uric acid in a patient in need thereof to treat a condition, said method comprising administering to said patient a therapeutically effective amount of a composition comprising allopurinol, or a pharmaceutically acceptable salt thereof, to achieve a uric acid level in the patient of 4 to 6 mg/dl, wherein said condition is hypertension.

18. (previously presented) A method for treating hypertension in a subject in need thereof, said method comprising administering to the subject a therapeutically effective amount of allopurinol, or a pharmaceutically acceptable salt thereof.

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EVIDENCE APPENDIX

EXHIBIT A: DECLARATION OF BERNARDO RODRIGUEZ-ITURBE, M.D., 32 pages. This declaration was submitted to the USPTO in this case on October 31, 2007 in conjunction with the filing of a Request for Continued Examination and Submission under 37 CFR § 1.114. On February 7, 2008, the Examiner issued a non-final office action following submission of this declaration. The Examiner acknowledges consideration of the declaration on page 7 of the February 7, 2008 office action.

EXHIBIT B: DECLARATION OF GEORGE BAKRIS, M.D. 35 pages

This declaration was submitted to the USPTO in this case on October 31, 2007 in conjunction with the filing of a Request for Continued Examination and Submission under 37 CFR § 1.114. On February 7, 2008, the Examiner issued a non-final office action following submission of this declaration. The Examiner acknowledges consideration of the declaration on page 7 of the February 7, 2008 office action.

EXHIBIT C: SECOND DECLARATION OF RICHARD J. JOHNSON, M.D. 4 pages

This declaration was submitted to the USPTO in this case on October 31, 2007 in conjunction with the filing of a Request for Continued Examination and Submission under 37 CFR § 1.114. On February 7, 2008, the Examiner issued a non-final office action following submission of this declaration. The Examiner acknowledges consideration of the declaration on page 7 of the February 7, 2008 office action.

EXHIBIT D: DECLARATION OF MATTHEW R WEIR, M.D. 4 pages.

This declaration was submitted to the USPTO in this case on December 10, 2007. On February 7, 2008, the Examiner issued a non-final office action following submission of this declaration. The Examiner acknowledges consideration of the declaration on page 7 of the February 7, 2008 office action.

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EXHIBIT A: DECLARATION OF BERNARDO RODRIGUEZ-ITURBE, M.D., 32 pages

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner	:	Kantamneni, Shobha
Art Unit	:	1617
Applicants	:	Kivlighn et al.
Serial No.	:	09/892,505
Filed	:	June 28, 2001
For	:	Treatment For Cardiovascular Disease

DECLARATION OF BERNARDO RODRIGUEZ-ITURBE, M.D.

I, Bernardo Rodriguez M.D., hereby declare and say as follows:

THAT, I am Professor of Medicine at Zulia University in Maracaibo, Venezuela, and President-Elect for the International Society of Nephrology. I am a world expert in the field of high blood pressure and nephrology (see my curriculum vitae attached) and have special expertise in animal models of hypertension. I am well versed with the work of Dr Johnson as I have collaborated with him on a variety of projects.

THAT, I am aware of the level of skill of one ordinarily skilled in the art of cardiovascular disease and kidney disease, and in particular, mechanisms of hypertension, hereto; AND being thus duly qualified declare as follows:

1. Much of my research has focused on animal models of hypertension, including studies in the SHR rat[1-4]. This is a hereditary model of hypertension that we and others have shown is mediated by oxidative stress. While I am aware that xanthine oxidase inhibitors have been reported to lower blood pressure transiently in this model[5] (also the Maeda Patent U.S. Patent 5,747,495), none of those studies suggested that this was due to uric acid, but rather asserted that this was due to oxidative stress. In fact, uric acid is considered an antioxidant and in some recent pilot studies we can show that it can lower blood pressure in these animals. Furthermore, most of the studies documenting oxidative stress in models of hypertension have focused on the role of NADPH oxidase, either produced by vascular cells[6,7] or by the inflammatory cells themselves[1-4].

2. Dr Johnson was the first, as far as I am aware, to propose uric acid as a cause of hypertension, and the first to provide experimental evidence[8]. Specifically, he was also the first to suggest targeting uric acid levels with xanthine oxidase (x.o.) inhibitors as a means for improving blood pressure. While x.o. inhibitors could have some effects on blood pressure via their antioxidant effects, the observation that they failed to lower BP in longterm studies in the SHR [9-11] taught away those skilled in the art from using them in patients with hypertension. Furthermore, as mentioned above, I believe that most of the oxidative stress in hypertension is due to a different system (NADPH oxidase) that is not inhibited by xanthine oxidase inhibitors.

3. I therefore conclude that the concept of lowering uric acid as a means to control blood pressure was a novel idea for which Dr Johnson brought forth the first direct experimental[8] as well as human[12] evidence. Studies in the SHR rat did not provide a reasonable expectation to those skilled in the art of successfully treating hypertension via administration of x.o. inhibitor, much less did they teach or suggest to those skilled in the art to use x.o. inhibitors as a means to lower blood pressure by reducing uric acid levels.

4. The undersigned declares further that all statements made herein of his own knowledge are true and that all statements made on information in belief are believed to be true; and further that these statements were made with the knowledge that willful false statements in the like so made are punishable by fine or imprisonment, or both, under §1001 of title 18 of the U.S.C. and that such willful false statements made jeopardize the validity of the application or of any patent issuing thereon.

Further declarant sayeth naught.

Bernardo Rodriguez-Iturbe

October 24, 2007

Date

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NACIONALITY (Country)	VENEZUELA
Wife:	MARIA TERESA ESPINOSA
Children:	MARIA TERESA, BERNARDO, PAULINA, DANIELA

Prsesent Academic Appointments

Profesor of Medicine	Facultad de Medicina, Universidad del Zulia, Maracaibo, Venezuela.
Medical Director, Renal Transplant Team	Hospital Universitario de Maracaibo, Maracaibo, Venezuela
Chief, Nephrology Service	Hospital Universitario de Maracaibo, Venezuela
Director, Postgrado Neprohology Residency Program	Universidad del Zulia, Facultad de Medicina, Div. de Estudios de Postgrado y Hospital Universitario de Maracaibo.
Director	Centro de Investigaciones Biomédicas, Instituto Venezolano de Investigaciones Cientificas –Zulia (IVIV-Zulia

Academic Degrees

M.D.	Facultad de Medicina, Universidad del Zulia, Maracaibo, Venezuela	1961
Master Medical Sciences	University of Pennsylvania Graduate School of Medicine, Philadelphia, Pa.	1967
Doctor Ciencias Médicas	Facultad de Medicina, Universidad del Zulia Maracaibo, Venezuela	1970

Past Academic Appointments	INSTITUTION	DATE
Coordinador-Director Postgraduate Studies Office Postgrado	Universidad del Zulia, Facultad de Medicina	1975-1978
School of Medicine Council Member	Universidad del Zulia, Escuela de Medicina	1974-1976 1978-1980
Faculty Council Member	Universidad del Zulia, Facultad de Medicina	1976-1979
Director	Instituto de Investigaciones, Biomédicas (INBIOMED)	1983-
Chief of Medical Clinic	Universidad del Zulia, Facultad de Medicina	1985-1987
Chairman of Department Medicine	Universidad del Zulia, Facultad de Medicina	1978-1980 1988-1989

Past Hospital Appointments		
Medical Director	Intensive Care Unit Hospital Universitario de Maracaibo	1968-1971
Director	Equipo de Trasplantes Renales Hospital Universitario de Maracaibo	1968-
Medical Director	Hospital Universitario de Maracaibo	1981-1983
Médico Jefe II	Servicio de Nefrología Hospital Universitario de Maracaibo	1983-

Other Institutions	INSTITUTION	DATE
Consultor	Organización Mundial de la Salud	Feb. 1972
Member Scientific Committe	Zulia Medical College	1969-1971
	Universidad del Zulia	1976-1979

Council Member	Consejo Nacional de Diálisis y Trasplante	1977-
Member, Committee for Clinical Medical Sciences . (Chairman)	Consejo Nacional Invest. Científicas y Tecnológicas (CONICIT)	1973-1978 1976-1978
Chairman, Task Force	Prersidential Task force for the Evaluation and Promotion of Science and Technology in Zulia region	1979
Council member, Postgraduate Studies	Consejo Nacional Invest. Científicas y Tecnológicas (CONICIT)	1983-1984
Council member,	Sistema de Promoción del Investigador (PPI)	1992-1996
Member	Academia de Ciencias de América Latina (ACAL)	1993-
Presidente FUNDASALUD	Gobernación, Estado Zulia	1994-1998
Delegado Principal CONICIT	Consejo Nacional de Universidades	1994-
Councilman	International Society of Nephrology	1995-2001
Member, Commission for the Global Advancement of Nephrology (COMGAN)	International Society of Nephrology Chariman, Latin American Subcommitte	1995-2005
President	Panamerican Society of Dialysis and Transplantation	1995-1997
Co-Director	Comité de Curriculum y Conocimientos Básicos de Nefrología, Sociedad Latinoamericana de Nefrología e Hipertensión	1996-1999
Miembro, Consejo de Apelaciones , Sistema de Promoción al Investigador (CONICIT)		2001-
Member, Prize and Awards Comission Latinamerican Society of Nephrology and Hypertension (SLANH)		2003
Member Fellowship Comité, Internacional Society of Nephrology		2004-2005

Awards during Medical School

Award for the highest academic score In Medical Studies	Escuela de Medicina Universidad del Zulia	1957-1958 1958-1959
Joaquín Esteva Parra Awards	Facultad de Medicina Universidad del Zulia	1959
Brancisco Eugenio Bustamante Award	Universidad del Zulia	1960
Graduation SUMMA CUM LAUDE	Facultad de Medicina, Universidad del Zulia,	1961

Postgradute Scholarships

Short-Term Scholarship	American College of Physicians	1973

Awards and Professional Recognitions

Prize CONICIT to the best Research paper	Consejo Nacional de Ciencia y Ciencia de la Salud Tecnología (CONICIT)	1977
Order Jesús Enrique Lossada	Universidad del Zulia	1986
Prize Scientific Merit	FUNDACITE-ZULIA	1986
Order Andrés Bello, For contributions to Science	República de Venezuela	1990
Research Award Francisco Eugenio Bustamante	Universidad del Zulia	1993
Prize for Clinical Investigation	Sociedad Venezolana de Nefrología	1993
Laureate Award	American College of Physicians	1995
PREMIO NACIONAL DE CIENCIA	Venezuela (CONICIT)	1998
PREMIO "LORENZO MENDOZA FLEURY"	Fundación Polar (Venezuela)	1999
PREMIO "VÍCTOR RAÚL MIATELLO" Sociedad Latinoamericana de Nefrología		1999
INTERNATIONA MEDAL,	National Kidney Foundation	2004

Luis Hernando International Prize in Nephrology	Fundación Iñigo Alvarez de Toledo	2007

Other Recognitions

Investigador Nivel IV Sistema de Promoción al Investigador (PPI)	1990
Doctorado Honoris Causa Universidad del Zulia	2001
International Fellow of The Council for High Blood Pressure Research	2002
Profesor Honoris Causa, Sociedad Mexicana de Hipertension Arterial	2006
Miembro de Honor, Sociedad Española de Nefrología	2006
Jose Strauss Award, Pediatric Nephrology Seminar, Miller School of Medicine, Miami University	2007

Editorial Board of Scientific Journals

Asesor Científico	INVESTIGACION CLINICA Maracaibo, Venezuela	1973-1982
Comité Editorial	REVISTA DE LA ACADEMIA DE MEDICINA, Maracaibo, Venezuela	1988-
Editorial Board	CLINICAL NEPHROLOGY München, Diesenhofen, FRG	1975-1995
Comité Editorial	CIENCIA, Facultad Experimental de Ciencias Maracaibo, Venezuela	1993-
Comité Editorial	NEFROLOGIA LATINOAMERICANA (Soc. Latinoamericana de Nefrologia)	1993-
Editor	KIDNEY INTERNATIONAL SPANISH AND PORTUGUESE	2005-
Editorial Board	AMERICAN JOURNAL OF KIDNEY DISEASES	2004- 2006
Advisory Board	NATURE, Clinical Practice Nephrology	2005
Editorial Board	Clinical Journal of the	

	American Society of Nephrology (CJASN)	2005-2006
Editorial Board	Current Opinion Nephrology and Hypertension	2007-2009

Medical and Postgraduate studies	INSTITUCION	FECHA
Estudios de Medicina	Facltad de Medicina Uiversidad del Zulia Maracaibo, Venezuela	1955-1961
Estudios de Postgrado	Postgraduate School of Medicine, University of Pennsylvania, School of Medicine, Philadelphia, PA.	1961-1962
Residencia Medicina Interna	Graduate Hospital, University of Pennsylvania, Philadelphia, PA.	1962-1965
Fellowship, Nefrologia	Graduate Hospital and University of Penssylvania, Medical Center, Philadelphia, PA.	1964-1966

Medical Societies
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Invited Conferences, Plenary lectures, Visiting Professorships
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Abstracts and presentations.
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PUBLICATIONS IN SCIENTIFIC JOURNALS

1. HENDERSON LW, RODRIGUEZ ITURBE B, BLUEMLE LW. Factors influencing b lood pH changes during extracorporeal hemodialysis in patients with chronic renal failure. *Trans Amer Soc Artif Intern Organs* 12:193-199, 1966.

2. RODRIGUEZ-ITURBE B, VERA G, RIVERA H, SERRANO H, SHAW HJ, GARCIA R. Homotrasplante renal. *Inves. Clin* 24:9-25, 1967.

3. RODRIGUEZ-ITURBE B. Evolución postoperatoria de los trasplantes renales. *Gaceta Médica de Caracas* 1:31-42, 1969.

4. RODRIGUEZ-ITURBE B, GARCIA R, MEDINA A, RUBIO L, SERRANO H. Curso postoperatorio del trasplante renal. *Acta Méd Venez* 16:99-103, 1969.

5. SERRANO H, RODRIGUEZ-ITURBE B. Estudio inmunológicos como ayuda en la detección del rechazo en el homoinjerto renal. *Invest Clin* 29:9-27, 1969.

6. RODRIGUEZ-ITURBE B, GARCIA R, RUBIO L. Diálisis crónica. Experiencia en el Hospital Universitario de Maracaibo. *Invest Clin* 31:7-43, 1969.

7. SERRANO H, RODRIGUEZ-ITURBE B, GARCIA R, CUENCA L. Complemento sérico en la glomerulonefritis aguda. *Invest Clin* 33:19-29, 1970.

8. RIVERA H, ALONZO A, RODRIGUEZ-ITURBE B, MATA H, GONZALEZ F, MOLERO M, BUCOBO E. Aspectos técnicos vasculares de los trasplantes renales. *Bol Soc Ven Cirugía* 24:717-722, 1970.

9. RODRIGUEZ-ITURBE B. Acute yellow phosphorus poisoning (Editorial). *New Engl J Med* 284:157, 1971.

10. RODRIGUEZ-ITURBE B, SERRANO H, GARCIA R, GALLEGOS B. Reliability of changes of serum complement, C3 and immunoglobulins during acute rejection of renal allografts. *Transplantation* 12: 405-407, 1971.

11. RODRIGUEZ-ITURBE B, GARCIA R, RUBIO L, ZABALA J, MOROS G, TORRES R. Acute glomerulonephritis in the Guillain-Barré-Strohl syndrome. Report of 9 cases. *Ann intern Med* 78:391-395, 1973.

12. RODRIGUEZ-ITURBE B, GARCIA R, RUBIO L, HENDERSON LW. Quantitation of hydrogen ion removal by extracorporeal hemodialysis in patiens with chronic renal failure. *Clin Nephrol* 2:238-244, 1974.

13. GARCIA R, RODRIGUEZ-ITURBE B, RUBIO L. Hemodiálisis en el hogar. Experiencia en el Hospital Universitario de Maracaibo. *Invest Clin* 16:143-163, 1975.

14. RODRIGUEZ-ITURBE B, GARCIA R, RUBIO L, TRESER G, LANGE K. Epidemic glomerulonephritis in Maracaibo. Evidence for progression to chronicity. *Clin Nephrol* 5:107-206, 1976.

15. LAYRISSE Z, PULIDO DE RODRIGUEZ M, RODRIGUEZ-ITURBE B, GARCIA E, STOILOW Z, SALAS G. Genetics of the HLA-A system in Venezuelan heterogenous population. *Vox Sang* 31:37-47, 1976.

16. GARCIA R, RODRIGUEZ-ITURBE B, RUBIO L, FERRER J. Hemodiálisis por doble cateterización de vena femoral. *Invest Clin* 17:122-127, 1976.

17. RODRIGUEZ-ITURBE B, GARCIA R, RUBIO L, SERRANO H. Immunohistologic findings in the lung in systemic lupus erythematosus. *Arch Pathol Lab Med* 101: 342-344, 1977.

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19. RODRIGUEZ-ITURB E B, GARCIA R, RUBIO L, LAYRISSE Z, MORALES E. Trasplante renal y diálisis crónica: estudios de sobrevida e histocompatiblidad. Incidencia de tuberculosis. *Invest Clin* 18:136-145, 1977.

20. RODRIGUEZ-ITURBE B. Algunos aspectos de la regulación renal de la tensión arterial. Revisión. *Invest Clin* 19(4): 156-181, 1978.

21. RODRIGUEZ-ITURBE B. Venezuela: Health Care and Medical Education. *Ann Intern Med* 88:125-126, 1978.

22. RODRIGUEZ-ITURBE B. Comentarios sobre la situación curricular de los estudios médicos en la Universidad del Zulia. *Acta Cientif Venez* 29:143-146, 1978.

23. RODRIGUEZ-ITURBE B, GARCIA R, WEBSTER GD, RUBIO L. Diálisis peritoneal y diuresis forzada en el tratamiento de la intoxicación por Glutethimida. *Invest. Clin* 19:87-101, 1978.

24. FERRER J, DIEZ-EWALDM, GARCIA R, RUBIO L, RODRIGUEZ-ITURBE B. Effects of triiodothyronine on the anemia of chornic renal failure. Am J Hematol 5:139-143,1978.

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28. RODRIGUEZ-ITURBE B, CASTILLO L, VALBUENA R, CUENCA L. Acute poststreptococcal glomerulonephritis. A review of recent developments. *Pediatrician* 8:307-324, 1979.

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39. RIVERA S, BELLOSO H, RINCON R, RODRIGUEZ-ITURBE B. Ensayo de inducción de tolerancia especifica a injertos de piel mediante trasplante de córnea en ratones. *Invest Clin* 24: 99-107, 1983.

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42. HENRIQUEZ-LA ROCHE C, RODRIGUEZ-ITURBE B. Infección del tracto urinario. Tópicos de importancia y tratamiento. Revisión. *Invest Clin* 25: 103-118, 1984.

43. COLINA-CHOURIO J, RODRIGUEZ-ITURBE B. Usos clínicos de los inhibidores de la enzima de conversión. Revisión. *Invest Clin* 25: 33-47, 1984.

44. MOSQUERA J, RODRIGUEZ-ITURBE B. Extracellular neuraminidase production of streptococci associated with acute nephritis. *Clin Nephrol* 21: 21-28, 1984.

45. RODRIGUEZ-ITURBE B. Epidemic poststreptococcal glomerulonephritis (Nephrology Forum). *Kidney Int* 25: 129-136, 1984.

46. RODRIGUEZ-ITURBE B. La historia natural de la nefritis postestreptocóccica. N Arch Fac Med 42: 457-460, 1984.

47. PARRA G, PLATT JL, FLAK RJ, RODRIGUEZ-ITURBE B, MICHAEL AF. Cell populations and membrane attack complex in glomeruli of patients with poststreptococcal glomerulonephritis: identification using monoclonal antibodies by indirect immunofluorescence. *Clin Immunol Immunopathol* 33: 324-332, 1984.

48. GARCIA RAMIREZ R, RUBIO L, RODRIGUEZ-ITURBE B. Indicaciones y contraindicaciones del trasplante renal.. Revisión. *Invest Clin* 25: 213-237, 1984.

49. MOSQUERA JA, KATIYAR VN, COELLO J, RODRIGUEZ-ITURBE B. Extracellular neuraminidase production of streptococci isolated from patients with glomerulonephritis. *J Infect Dis* 151:259-263, 1985.

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51. WONG A, GARCIA R, HERIQUEZ C, RODRIGUEZ-ITURBE B. Salmonella osteomyelitis in a renal trasplant recipient. Brief Report. *Invest Clin* 26 (4): 231-234, 1985.

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53. RODRIGUEZ-ITURBE B. The functional reserve capacity of the kidney. *Int J Artf Org* 9 (2): 81-84, 1986.

54. MOSQUERA J, RODRIGUEZ-ITURBE B. Glomerular binding sites for peanut agglutinin in acute poststretococcal glomerulonephritis. *Clin Nephrol* 26 (5): 227-234, 1986.

55. HERRERA J, GARCIA R, RODRIGUEZ-ITURBE B. Parasitosis in the immunosuppressed host. Review. *Invest Clin* 28 (1): 47-59, 1987.

56. COOK GA, RODRIGUEZ H, SILVA H, RODRIGUEZ-ITURBE B, BOHORQUEZ H. Adult respiratory distress secondary to strongyloidiasis. *Chest* 92: 1115.116, 1987.

57. HERRERA J, GARCIA R, RUBIO L, HENRIQUEZ C, RODRIGUEZ-ITURBE B. Sobrevida actuarial en trasplante renal: Hospital Universitario de Maracaibo (1967-1986). *Invest Clin* 28(3): 133-142, 1987.

58. NAVARRO JA, GARCIA R, RUBIO D, RODRIGUEZ-ITURBE B, VIRLA J, MENDEZ G, ROMERO R. Correlación de los niveles de aluminio en agua, sangre completa y dializado de pacientes en hemodiálisis crónica. *Invest Clin* 28(3) 153-163, 1987.

59. RODRIGUEZ-ITURBE B, HERRERA J, GARCIA R. Relationship between glomerular filtrtion rate and renal blood flow at different levelvs of protein-induce hyperfiltarion in man. *Clin Sci* 74:11-15, 1988.

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63. HERRERA J, RODRIGUEZ-ITURBE B, PARRA G, COELLO J, GARCIA R, COLINA-CHOURIO J, SINAIKO A. Urinary prostaglandin E and Kallikrein activity in glomerular hyperfiltration induced by a meat meal in man. *Clin Nephrol* 30(3): 151-157, 1988.

64. GARCIA R, MARTINEZ J, SMITH R, HENRIQUEZ C, ZSCHAEK D, HERRERA J, RODRIGUEZ-ITURBE B, DOMINGUEZ J. Evaluación de donantes de riñón 1 a 10 años después de nefrectomia. *Invest. Clin* 29: 61-70, 1988.

65. RODRIGUEZ-ITURBE B, HERRERA J, GUTKOWSKA J, PARRA G, COELLO J. Atrial natriuretic factor increases after a protein meal in man. *Clin Science* 75:495-498, 1988.

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75. MOSQUERA J, RODRIGUEZ-ITURBE B, PARRA G, NARVAEZ E. Fish oil dietary supplementation reduces la expression in rat and mouse peritoneal macrophages. *Clin Immunol Immunopathol* 56: 124-129, 1990.

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Book Chapters

RICHARD J. JOHNSON, BERNARDO RODRIGUEZ-ITURBE, DUK-HEE KANG, AND JAIME HERRERA-ACOSTA. Pathogenesis and Clinical Course of Essential Hypertension. In Comprehensive Clinical Nephrology, Third Edition, Edited by Johnson RJ, Floege J, Feehally J. Mosby Publishers (in press)

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EXHIBIT B: DECLARATION OF GEORGE BAKRIS, M.D. 35 pages

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner	:	Kantamneni, Shobha
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Applicants	:	Kivlighn et al.
Serial No.	:	09/892,505
Filed	:	June 28, 2001
For	:	Treatment For Cardiovascular Disease

DECLARATION OF GEORGE BAKRIS, M.D.

I, George Bakris M.D., hereby declare and say as follows:

THAT, I am Professor of Medicine and Director of the Hypertensive Diseases Center at the University of Chicago, Pritzker School of Medicine. I am a recognized world expert in the field of high blood pressure (see my curriculum vitae attached) and am also a member and coauthor of the Joint National Committee 7 on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure [1] which provides the primary guidelines for blood pressure management in the United States. I am well versed with the work of Dr Johnson as I have followed it from its beginnings in the mid to late 1990s and have also been moderator for many of the lectures he has given, including overseeing a debate on the role of uric acid that he had with members from the Framingham Heart Study group.

THAT, I am aware of the level of skill of one ordinarily skilled in the art of cardiovascular disease and kidney disease, and in particular, mechanisms of hypertension, d hereto; AND being thus duly qualified declare as follows:

1. Based on his experimental studies, Dr Johnson was the first to propose uric acid is a cause of hypertension[2]. The novelty was the concept that uric acid caused hypertension, for the association had already been established. The longstanding belief, based on studies such as the Framingham Heart Study[3], was that elevated uric acid in hypertension was a secondary phenomenon and not causative of hypertension. Moreover, the notion of prescribing medicines to lower uric acid for treating hypertension would have been considered, by experts in the field, as an improper and wasteful medical practice. As

such, we did not list uric acid as a risk factor for hypertension in the JNC7 report, nor was this done by any other major society.

2. I am aware that there were earlier studies in which it was reported that xanthine oxidase inhibitors could lower blood pressure in the spontaneously hypertensive rat (SHR)[4]. The authors of the SHR studies always thought that the xanthine oxidase inhibitors were functioning as antioxidants since they block xanthine oxidase-generated oxidants. In particular, never was efficacy linked with targeting uric acid levels to certain ranges. Moreover, the concept that these agents might be useful to treat hypertension was thwarted by the fact that these inhibitors did not lower BP in longterm studies in the SHR[5-7]. Incidentally, it should be noted that antioxidants have largely failed in the treatment of hypertension[8]. This does not mean that oxidants produced by xanthine oxidase may be important, for they could possibly play a role in hypertension. However, whether or not this occurs, the studies conducted in the SHR rat prior to 2001 did not provide a motivation to those skilled in the field to administer xanthine oxidase inhibitors to lower uric acid to a certain level as a means to lower hypertension. It bears repeating that controlling uric acid as a means to control hypertension was originally suggested by Dr. Richard Johnson.

3. I have read the editorial published in 1998 by Ward[9] which is a mini-review of the theories concerning uric acid discussed in the literature at that time: some suggesting uric acid is a risk factor and some suggesting that uric acid is protective. The Ward paper does not assert either way whether uric acid is a risk factor or protective. The Ward paper clearly does not hypothesize nor suggest that uric acid plays a causative role in hypertension. It is important to understand that those skilled in the art of science and medicine are careful to not confuse something considered as a risk factor with something that is a causative factor. As an example, let's assume that a study finds that drinking alcohol is a risk factor associated with lung cancer. Those skilled in the art would not assume from this that drinking alcohol causes lung cancer (the medical community would undoubtedly interpret this study to mean that many people who drink also smoke). Likewise, when Ward or any similar paper in the literature prior to the Framingham Heart

Study discussed the possibility of uric acid as being a risk factor for hypertension, this was not interpreted to mean that uric acid caused hypertension. The only way to determine whether drinking alcohol causes lung cancer or to determine whether uric acid causes hypertension is to test the hypothesis by conducting a scientific study. The study conducted in the paper published by the Framingham Heart Study Group[3] was directly tailored to examine the same theories regarding uric acid that were discussed by Ward. As alluded to above, the Framingham Heart Study Group emphatically concluded that uric acid does not have a causative role in cardiovascular disease. Furthermore, prior to Dr Johnson's work there was no proposed mechanism(s) by which uric acid might cause hypertension. Accordingly, the Ward paper itself did not provide a motivation in the art to control uric acid levels as a means to control hypertension.

4. The undersigned declares further that all statements made herein of his own knowledge are true and that all statements made on information in belief are believed to be true; and further that these statements were made with the knowledge that willful false statements in the like so made are punishable by fine or imprisonment, or both, under §1001 of title 18 of the U.S.C. and that such willful false statements made jeopardize the validity of the application or of any patent issuing thereon.

Further declarant sayeth naught.

[name]

October 17, 2007

Date

1. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, Jr., Jones DW, Materson BJ, Oparil S, Wright JT, Jr., Roccella EJ. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *Jama* 2003;289:2560-72.
2. Mazzali M, Hughes J, Kim YG, Jefferson JA, Kang DH, Gordon KL, Lan HY, Kivlighn S, Johnson RJ. Elevated uric acid increases blood pressure in the rat by a novel crystal-independent mechanism. *Hypertension* 2001;38:1101-6.
3. Culleton BF, Larson MG, Kannel WB, Levy D. Serum uric acid and risk for cardiovascular disease and death: the Framingham Heart Study. *Ann Intern Med* 1999;131:7-13.
4. Miyamoto Y, Akaike T, Yoshida M, Goto S, Horie H, Maeda H. Potentiation of nitric oxide-mediated vasorelaxation by xanthine oxidase inhibitors. *Proc Soc Exp Biol Med* 1996;211:366-73.
5. Laakso J, Mervaala E, Himberg JJ, Teravainen TL, Karppanen H, Vapaatalo H, Lapatto R. Increased kidney xanthine oxidoreductase activity in salt-induced experimental hypertension. *Hypertension* 1998;32:902-6.
6. Maenishi O, Ito H, Suzuki T. Acceleration of hypertensive cerebral injury by the inhibition of xanthine-xanthine oxidase system in stroke-prone spontaneously hypertensive rats. *Clin Exp Hypertens* 1997;19:461-77.
7. Trachtman H, Valderrama E, Futterweit S. Nephrotoxicity of allopurinol is enhanced in experimental hypertension. *Hypertension* 1991;17:194-202.
8. Ward NC, Croft KD. Hypertension and oxidative stress. *Clin Exp Pharmacol Physiol* 2006;33:872-6.
9. Ward HJ. Uric acid as an independent risk factor in the treatment of hypertension. *Lancet* 1998;352:670-1.

C U R R I C U L U M V I T A E

PERSONAL INFORMATION

NAME: George Louis Bakris, M.D., F.A.C.P., F.A.H.A, F.A.S.N

DATE OF BIRTH: June 15, 1952

BIRTHPLACE: Athens, Greece

CITIZENSHIP: U.S.A.

HOME ADDRESS: 1420 Wellington Terrace, Munster, IN 46321

BUSINESS ADDRESS: University of Chicago Pritzker School of Medicine,
Department of Medicine, Hypertensive Diseases Center, Section of Endocrinology, Diabetes and Metabolism, 5841 S. Maryland Ave., MC 1027, Room P-328A, Chicago, IL 60637
Administrative Asst.-Barbara-773.702.7936; FAX: 773.834.0486;
Direct Line-773.702.7930; email: gbakris@earthlink.net

MARITAL STATUS: Married, wife - Demetria
Two Children - Athena, 1986; Louis, 1991

EDUCATION

Undergraduate: Indiana University, Bloomington, IN
DEGREE: B.A., Biology and Psychology, 1974
Graduate: University of Chicago, Chicago, IL
DEGREE: M.A., Human Development, 1975
Thesis- Hypothalamic-Pituitary-Adrenal Axis & Norepinephrine Metabolism in Depressive Illness; Advisor - John M. Davis, M.D.
Medical School: University Health Sciences/Chicago Medical School, No. Chicago,
DEGREE: M.D., Medicine, 1981

POSTGRADUATE CLINICAL AND RESEARCH TRAINING

Internship: *Internal Medicine*, 4/81-4/82
Mayo Graduate School of Medicine, Rochester, MN, Advisor - Randall Vollersten
Residency: *Internal Medicine*, 4/82-6/82
Mayo Graduate School of Medicine, Rochester, MN; Advisor - Randall Vollersten
Residency: *Psychiatry, 7/82-6/83*
Washington University School of Medicine, St. Louis , MO- Samuel Guze
Research Fellowship: Renal Physiology and Hypertension, 7/83-9/84

Mayo Graduate School of Medicine, Rochester, MN; Advisor - John C. Burnett, Jr.
Residency: *Internal Medicine,* 9/84-6/86
University of Illinois at Chicago; Advisor-Ruy Lorenzo
Fellowship: *Nephrology*, 7/86-6/88
University of Chicago Medical Center, Chicago, IL; Advisor - Adrian Katz
Fellowship: *Clinical Pharmacology*, 7/86-6/87
University of Chicago Medical Center, Chicago, IL; Advisor - Leon Goldberg,

PAST AND CURRENT ACADEMIC APPOINTMENTS

Current:
Professor of Medicine; *Director*, Hypertensive Diseases Center, Section of Endocrinology, Diabetes and Metabolism, University of Chicago Pritzker School of Medicine, 8/06-present

Past:
Professor (tenured), Departments of Preventive Medicine and Internal Medicine; Vice-Chairman, Department of Preventive Medicine; Director, Hypertension/ Clinical Research Center -1/99-6/06
Director and Founder of Rush Hypertension Fellowship Program-6/93-6/06
Lecturer- Division of Nephrology, University of Illinois Medical Center 1/94-6/07
Associate Professor (tenured), Departments of Preventive Med and Internal Med 12/96-12/99
Assistant Professor, Departments of Preventive Med and Internal Med;4/93-12/96
Assistant Professor of Medicine and Pharmacology, Division of Nephrology & Director of Renal Fellowship Program University of Texas Health Science Center at San Antonio, 8/91 - 3/93
Staff Nephrologist and *Director of Renal Research*, Ochsner Clinic, New Orleans, LA- 8/88-7/91
Assistant Professor of Medicine, Section of Clinical Pharmacology, Tulane University School of Medicine, New Orleans, LA, 10/88 -7/91
Adjunct Assistant Professor of Physiology & Pharmacology, Tulane University School of Medicine, 10/88-7/91

BOARD CERTIFICATION:

Diplomate- National Board of Medical Examiners, 1982
Diplomate- American Board of Internal Medicine
Internal Medicine, September, 1986 (106504)
Diplomate- American Board of Internal Medicine
Nephrology, November, 1992 (106504)
Clinical Hypertension Specialist- Am. Society of Hypertension, 1999

LICENSURE:

Illinois	1986	Permanent	036-064409
Louisiana	1988	Permanent	07707 (Inactive)
Texas	1992	Permanent	J0912 (Inactive)

HONORS AND AWARDS:

Listed In America's Top Doctors-2006 &2007
Hellenic Medical Society of New York-Distinguished Physician Award, 2003
American Diabetes Association (Illinois Affiliate)-Father of the Year Award-2003
National Kidney Foundation of South Texas Award-For help organizing and making operational the San Antonio chapter, 1993
National Kidney Foundation National Award- Comprehensive Excellence in Medical Education, Boston, 1993
Chicago Medical School Scholastic Award 1981[This award is given to the student who had the highest grades on his/her clinical rotations].
Chicago Medical School, Dean's Award [This award is given to the top ten medical students of graduating class that have demonstrated outstanding scholastic achievement and best exemplify the ideals of the school.] 1981
Alpha Omega Alpha Medical Honor Society
Graduated in the upper 10% percent of medical class

PROFESSIONAL ORGANIZATIONS:

Fellow of:

American Society of Nephrology
American College of Clinical Pharmacology
The American College of Physicians
The American Heart Association (Council for the Study of High Blood Pressure Council on the Kidney)

Member of

The American Society of Nephrology
The International Society of Nephrology
Central Society for Clinical Research
National Executive Boards
Board of Reagents -American College of Clinical Pharmacology (1996-2005)
Hypertension Executive Council-National Kidney Foundation (1996-1999);(Chairman)-(1998-1999)
Member of National Kidney Foundation-President's Council (1999-present)
National High Blood Pressure Education Council (NHLBI-NIH)-JNC (2000-present)

EDITORIAL BOARDS:

Editor: Am. J of Nephrology (6/02-present)
Hypertension Section Editor: Up-To-Date - (7/06-present)

Associate Editor:

J Human Hypertension-(6/2007-present)
www.thekidney.org (Hypertension, Section Editor)-(6/2004-present)
Am. J Kidney Disease (1/02-6/04)
Translational Med. (7/01-present)

Kidney: Current Survey of World Lit. (10/93-1/2002)
J Clinical Pharmacology-Renal Section Editor (1/93-present)
Postgraduate Medicine - Nephrology Section Editor (1/92-present)

Member

Diabetes Care (2007-2009)
J of the Cardiometabolic Syndrome-(11/2005-present)
Advances in Chronic Kidney Disease (1/2003-present)
Am J Hypertension (11/99-2003)
Kidney International (7/99-1/02; 1/05-present)
Cardiovascular Drugs and Therapy (1/99-present)
J of Nephrology (1/97-present)
Hypertension (1/97-1/02; 1/03-present)
Hypertension, Dialysis & Clinical Nephrology (HDCN)-Internet J. (6/96-present)
Journal of Human Hypertension (12/94-present)
Journal of Diabetes and Its Complications (7/91-present)
Nephrology, Dialysis and Transplantation (1/02-present)

GUEST EDITOR: **TOPICS**

J Clinical Pharmacology–(Progression of Diabetic Renal Disease)- 4/95
J Human Hypertension – (The Lanai Symposium)-1/97
Coronary Artery Disease- (Renal Disease in the Elderly)-12/1997
Hypertension, Renal Section (Supplement to Annual HBPC Meeting)-1/1998
Mineral and Electrolyte Metabolism- (Renin Angiotensin System & Kidney In Diabetes)-January, 1999

ACADEMIC COMMITTEES (Past and Present)

Member, Research Advisory Committee, Ochsner Clinic (1/89-6/91)
Member, Medical Advisory Panel/Hypertension in Blacks - National Institutes of Health (NIDDK) [10/91-1/92]
Grant Reviewer-American Heart Association and National Kidney Foundation-National/Local (1991-present)
Chairman-Diabetic Nephropathy-Clinical, Program Committee, American Society of Nephrology Meeting- 1990,1992,1999
Co-Chairman- American Heart Assoc. Council on the Kidney-National Meeting. Preventing Progression of Diabetic Renal Disease- Dallas, TX, 1991
National Organizing Committee and Chairman of Symposium "Approaches to the Treatment of Diabetic Renal Disease", Am College of Clin Pharmacol (11/93)
Consultant-Cardio-Renal Advisory Board [FDA]-(1993-2002)
Member, Ad Hoc Review Committee for Program Projects-NHLBI [National Institutes of Health, 1992,1995,1997,1999, 2000
Clinical Research Center (GCRC) Review Committee, University of Texas Health Science Center, San Antonio (4/92-4/93)
Member-National High Blood Pressure Education Program Working Group on

Hypertension and Renal Disease - NIH (Heart, Lung and Blood Institute)1994
Program Committee- AHA Blood Pressure Council (1996-1999)
Writing Member, The Joint National Committee of the High Blood Pressure Education Program Working Group (JNC VI), NIH- 1997
Chairman-Clinical Outcomes/Trials Program Committee, American Society of Nephrology Meeting- 1997
Master's of Science in Clinical Research Program-(NIH K30) (Co-Principal Investigator) -Rush University Medical Center (1999-2005)
Postgraduate Education Comm.-Am. Society of Nephrology (ASN)(2000-2006)
Program Committee, Chairman- National Kidney Foundation-Annual Meeting (1998-2000)
Executive Committee Member, The Joint National Committee of the High Blood Pressure Education Program Working Group (JNC 7), NIH (NHLBI)- 2002-2003
NIH Clinical Trials Study Section-Ad hoc member (1999-2003)
Rush University Continuing Medical Education Committee (2002-2006)
American College of Clinical Pharmacology CME Committee (2000-present)

ADMINISTRATIVE POSITIONS IN NATIONAL ORGANIZATIONS (Past and Present)

USP Nephrology/Urology Expert Committee-Member-2007-present
Chairman, Complications Committee-*American Diabetes Assoc.* (2004-2005 &06-07)
Member/Vice-Chair, Institutional Review Board (IRB), *Rush University Medical Center-* (1998-2000)
Member, Executive Research Council, *Am. Heart Assoc.*-IL Affiliate, 1995-1998
Medical School Admissions Committee, *Rush Medical College* 1994-1997,
Chairman, (1996-1997)
National Kidney Foundation, Illinois Affiliate Medical Advisory Board, Executive Committee, Chicago, 1995-present
Member, Accreditation Committee, Louisiana State Continuing Medical *Education* (CME) Board (12/89-7/91)
Board of Directors, *National Kidney Foundation of Texas*(2/92-4/93)
Member: Board of Regents- *Am. College of Clinical Pharmacology* (1997-2005)
President, Hellenic Medical Society of Chicago, 1999-2000
President, American College of Clinical Pharmacology, 2000-2002.
Board of Directors, Member-International Soc. of Hypertension in Blacks (ISHIB)-2001-present

Listed in:

Top Physician's in America-2006, 2007
Who's Who in the World-2002-present
Who's Who (National Registry)-2002-present
Who's Who in Medicine and Healthcare-2001-present
Sterling's Who's Who in America-1999-present
Scientific Committees of the American Heart Association-1991-present
Who's Who In Diabetes (American Diabetes Association) -1999-present

RESEARCH ACTIVITIES

Current:

Relationships between changes in vascular compliance and blood pressure reduction with agents that inhibits inflammatory cytokines.

Clinical Trials that evaluate the effects of different antihypertensive therapy on kidney disease progression and cardiovascular outcomes

Previous:

Progression of diabetic renal disease: a) mechanisms of proteinuria (effects of drugs on glomerular permeability and changes in mesangium), b) development of clinical trials of renal disease progression and focus on lipid metabolism

Mechanisms of radio-contrast medium induced renal dysfunction.

Pharmacological effects of drugs on renal hemodynamics

Effects of vasoactive growth factors (ANG II,AVP,ET), insulin and glucose on the glomerular mesangial cell proliferation.

GRANT SUPPORT (current and previous)

National- G. Bakris-(Principal Investigator).

Admixture Mapping to Examine the Genetics of Hypertensive Kidney Disease in African-Americans- NIDDK (Co-Investigator)- submitted (2006)

AASK Cohort Study (African-American Study of Kidney Disease)- [UO1] (4/02-6/07)= $1.5million

K30-Clinical Research Center Training Grant –Co-P.I. (7/99-7/05)-$1 million

National Institutes of Health (NIDDK)-[U01 DK48643] (7/94-7/02)- *Progression* of Renal Disease in African Americans (AASK Trial)- $3.2 million

National Institutes of Health (NHLBI)-[1P50HL55007-01] (2/96-1/01)- *Genetics* of Hypertension in African-Americans-SCOR Grant-(Clinical Center) –Co-Investigator- PI Richard Lifton-Yale University- $400,000

American Assoc. of Kidney Patients (12/88-12/89) - Effects of insulin and glucose on human mesangial cell mitogenesis and endothelin production-$20,000.

Boehringer-Ingelheim- Research Fellowship in Clinical Pharmacology-1987-$60,000

National Institutes of Aging (NIA)- Psychological and physiologic changes during the menopausal transition (Consultant)- (1995-1997)- $7500- 3% effort

National Institutes of Health, NIDDK (1995-1997).Genetic Determinates of Nephropathy in NIDDM (Consultant) 10% effort-$10,000/year-salary support.

National Institutes of Health, NIDDK [U01] (9/91-3/93) - Modification of Diet in Renal Disease (MDRD Trial) (co-investigator) - $25,000/year, salary support

Local and Regional Grants - G. Bakris (Principal Investigator)

Alton Ochsner Medical Foundation Award (12/1/88-11/30/92) - The renal hemodynamic and cellular effects of calcium antagonists and converting enzyme inhibitors in diabetic dog - $150,000.

American Heart Association, Louisiana Affiliate (7/90-6/91) - The effects of arginine vasopressin on mesangial cell growth and endothelin production in various glucose milieus -$14,974.

American Diabetes Association, Louisiana Affiliate (7/89-6/90) - The effects of various hormones and glucose milieus on human mesangial cells growth - $10,000.

Noel Foundation Research Award of the National Kidney Foundation of Illinois (1986-1987)-The role of oxygen free radical generation in radiocontrast medium-induced decreases in glomerular filtration rate - $20,000

National Kidney Foundation of the Upper Midwest (7/1/84-6/30/85) – The contribution of oxygen free radicals in radiocontrast medium-induced renal hemodynamic changes - $10,000

Investigator-Initiated Studies (Pharma. funding) -G. Bakris (Principal Investigator)

The protective effects of calcium antagonists on radiocontrast medium induced renal dysfunction -$90,000.(1/87-1/88)

The renal effects of calcium antagonists and angiotensin converting enzyme inhibitors in the diabetic dog -$60,000. (3/89-2/91)

A double blind placebo controlled multicenter trial evaluating the effects of misoprostol on renal hemodynamics following non-steroidal and anti-inflammatory drugs in diabetic man- $130,000. (4/90-4/91)

The effects of combined therapeutic agents(calcium antagonists & ACE inhibitors) on renal preservation and proteinuria in diabetic subjects-$149,000 (3/92-3/94)

The effects of different classes of calcium antagonists on glomerular permselectivity- $300,000 (3/92-12/94)

The effects of similar classes of calcium antagonists on renal hemodynamics and albuminuria in type 2 diabetic patients –$100,000 (5/92-4/93)

Double Blind Randomized Trial comparing the effects of different classes of calcium antagonist on changes in glomerular morphology in a remnant kidney model in the rat.-$175,000 (1/95-6/97)-

Effects of combination therapy compared to either benezapril or amlodipine versus losartan on progression of glomerulosclerosis-$109,000 (1997-1998)

The effects of valsartan on potassium homeostasis in patients with renal insufficiency-randomized, crossover, multicenter study -$150,000 (8/97-8/99)

The effects of Lotrel on LDL cholesterol sub-fraction and glomerular permeability; a multicenter study -$190,000 (9/97-9/99)-

The Effects of Nonionic versus Ionic Contrast Media on Renal Function: A double-blind trial, co-investigator- $200,000 (6/89-6/91)

A Double-Blind, Randomized, Placebo-Controlled, Multicenter Trial To Evaluate the Safety and Efficacy of Intravenous Auriculin Human Atrial Natriuretic Peptide in the Treatment of Acute Tubular Necrosis. (PI)- 60,000. (3/93-3/94)

INVEST Trial (International Verapamil SR-Trandolopril Study) Co-Investigator,

Regional Director. (7/97-2002)

The comparative effects of a COX2 inhibitor versus a COX1 inhibitor on renal function and blood pressure-120,000 (2000-2001)

The comparative effects of an ACE I or ARB on potassium homeostasis- Merck-140K (1999-2001)

The comparative effects of an ACE inhibitor, ARB or combination on proteinuria reduction when controlling for blood pressure reduction-King Pharma- 2003-2004 ($135K)

Comparison of the long term effects of different beta blockers on components of the metabolic syndrome-The GEMINI Trial-Principal Investigator- 2003-2004 Glaxo Smith Kline-(150K)

Comparison of Different type of Combination Antihypertensive Therapy on Insulin Resistance and the Metabolic Syndrome-The STAR Trial-Principal Investigator-Abbott Labs –(2003-2005)-(100K)
Effects of PPAR gamma on inflammatory factors in metabolic syndrome-GSK (400K)-2007-2008)

NATIONAL/INTERNATIONAL CLINICAL TRAIL EXECUTIVE COMMITTEES:

VALUE
INVEST
ACCOMPLISH

DATA SAFETY MONITORING BOARDS-National Clinical Trials

CHICAGO trial-2003-2006
PERISCOPE-2003-2007
TAKEDA-Neuropathy Trail-Chair 2006-2007

TEACHING ACTIVITIES:

- Physical Diagnosis (basic and advanced)-Tulane University (8/89-6/91); University of Texas Health Science Center (8/91-3/93).
- Renal Pathophysiology lecture series (yearly) (8/91-3/93); University of Texas Health Science Center Nutrition lecture series (junior and senior medical students) (8/91-3/93); University of Texas Health Science Center at San Antonio
- Clinical Pharmacology Lecture Series (senior medical students/graduate students) (8/89-6/91)-Tulane University Medical School.
- Coordinator of the Renal Section - American College of Physicians -Update in 'Internal Medicine - (1992-1993)
- Coordinator of Renal Fellowship Training Program and Lecture Series- University of Texas Health Science Center at San Antonio (12/91-3/93)
- Coordinator of the Hypertension/Clinical Research Fellowship Training Program -Rush Presbyterian/St. Luke's Medical Center (4/93-present)
- Preventive Medicine/Hypertension Grand Rounds Director (1995-2002)
- Pathophysiology Lecture Series in Hypertension-Rush Medical College, Chicago(1/94-1/99)
- Annual Kidney Disease/Hypertension Lecture Series-Rush Graduate School of Nursing (1999-2006)
- Pathophysiology Lecture Series in Nephrology-University of Illinois Medical Center (1995-2000)
- Clinical Trials Course Director- for M. Sc. in Clinical Research Degree (K30)-Course Director-1999-2006)
- Harvard Nephrology Annual Board Review Update Course Lecturer (2000-2007)

POSTDOCTORAL FELLOWS SUPERVISED:

(* indicates academic appointments post fellowship)

1989-1991 Richard Slataper, MD*- *Oscher Clinic-Baton Rouge, LA*
1989-1990 Edward Sauter, MD**-Assoc. Professor-MUSC*

1989-1991	Brian Demarie, MD-*Practice*
1990-1991	Vernon Valentino, MD-*Practice*
1990-1991	Bradley Barnhill, MD-*Practice*
1991-1993	Dan Riley, MD* *Assoc Professor- U Texas Health Science Center-San Antonio*
	Kevin Abbott, MD**-Professor & Director Clinical Nephrology-USHOES*
1993-1994	David Hoelscher, MD-*Practice*
1994-1995	Amy Mangrum, MD*, *Asst. Professor-UVA-Charolettesville*
	Luke Kusmirek, MD**-Asst. Professor-U of Kentucky*
1995-1996	Jung Yi, MD -*Practice*
1996-1997	Kostantinos Makrilakis, MD,PhD**-Assoc. Professor-U of Athens School of Medicine-GREECE*
1997-1998	Imelda Villarosa, MD,-*Practice*
	Nauman Tarif, MD**-Assoc. Professor-Medical School PAKISTAN*
1998-1999	Visclaw Drincic, MD-*Geriatrics Practice*
1999-2000	Unini Odama, MD-*Endocrinology Practice*
2000-2001	Munivar Izhar, MD**-Asst. Prof.-Rush Medical College*
2001-2002	Jay Garg, MD**-Industry*
2002-2003	Nicholas Kaperonis, MD-*Asst. Professor (GREECE)*
2002-2003	Renee Ellis, MD**-Nephrology Practice*
2003-2004	David Chua, MD**-Instructor-UVA-Charolettesville*
2004-2005	Ken Choi, MD-*Practice*
2005-2006	Nitin Khosla, MD-*Postdoctural Fellow-UCSD*
2005-2006	Pantrelis Sarafidis, MD**-Postdoctural Fellow (GREECE)*
2006-2007	Atul Chugh, MD-
2007-2008	Irene Duka, MD

PUBLICATIONS - Original Papers

1. BAKRIS GL: Existential Psychology: A review. **J Instructional Psych.** 1977; 4: 13-20.
2. BAKRIS GL, Vernasco K, Verongas D:The consistency model of personality: An overview. **J Instructional Psych** 1980;7:71-76.
3. BAKRIS GL, Smith DW, Tiwari S: Dermatologic manifestations of lithium: A review **International J. of Psychiatry in Medicine** 1981;10:327-331.
4. BAKRIS GL, Taylor MA, Mulopulos GP, Wawczak S: Lithium prophylaxis and the kidney. **J. of Affective Disorders** 1981;3:37-42.
5. Tiwari S, BAKRIS GL: Psychogenic vertigo:A review. **Postgraduate Med**. 1981; 70:69-77
6. BAKRIS GL, Mulopulos GP, Tiwari S, Franklin C: Orphenadrine citrate: An alternative for muscle contraction headaches. **Illinois Med J** 1982;161:106-108.
7. BAKRIS GL: Clonidine for opiate withdrawal in the chronic pain patient. **Postgraduate Medicine** 1982; 71:240-241.
8. BAKRIS GL, Cross PD, Hammarsten J: The use of clonidine for management of opiate abstinence in a chronic pain patient. **Mayo Clinic Proc** 1982;57:657-660

9. Petruccelli B, BAKRIS GL, Miller T, Korpi E, Linnoila M: A liquid chromatographic assay for 5-hydroxy-tryptophan, serotonin and 5-hydroxyindoleacetic acid in human body fluids. **Acta Pharmacol et Toxicol** 1982;51:421-427.
10. BAKRIS GL, Mulopulos GP, Horchik R, Ezdinli EZ, Ro J, Yoon B: Pulmonary scar carcinoma: A clinic-pathologic analysis. **Cancer** 1983;52:493-497.
11. BAKRIS GL, Cross PD, Hammarsten J: Disopyramide associated liver dysfunction. **Mayo Clinic Proceedings** 1983;58:265-267.
12. BAKRIS GL, Zorumski CF: Chronic Pain: A pharmacologic review and behavior modification approach. **Postgraduate Medicine** 1983;73:119-128.
13. Zorumski CF, BAKRIS GL: Lithium associated choreoathetosis: A case report and literature review. **Am J Psychiatry** 1983;140:1621-1622.
14. BAKRIS GL, Burnett JC, Jr.: A role for calcium in radiocontrast-induced alterations in renal hemodynamics. **Kidney International** 1985;27:465-468.
15. BAKRIS GL, Wilson DM, Burnett JC, Jr The renal forearm and hormonal responses to standing in the presence and absence of propranolol. **Circulation** 1986;74: 1061-1065.
16. Arend L, BAKRIS GL, Burnett JC, Jr., Megerian C, Spielman WS: A role for intra-renal adenosine in the renal hemodynamic response to contrast medium. **J. Lab. Clin. Med**. 1987;110:406-411.
17. BAKRIS GL, Weber R, Nelson K, Elliott W, Kaplan E, Murphy MB: Comparison of the effects of dopamine and fenoldopam, a selective dopamine-1 agonist, on parathyroid hormone release in man. **Mineral and Electrolyte Metabolism** 1988; 14(6):343-346.
18. BAKRIS GL: The effects of oral ingestion of a nitroglycerin transdermal patch. **JAMA** 1988; 260:1243-1244.
19. BAKRIS GL, Kern S:The clinical spectrum of nonsteroidal anti-inflammatory drug-induced renal dysfunction: A review. **Am. Family Physician** 1989; 40(4):199-204.
20. BAKRIS GL, Frohlich ED: Early identification of target organ damage in man with essential hypertension. **Practical Cardiology** 1989;15(5):60-76.
21. BAKRIS GL, Frohlich ED: The evolution of antihypertensive therapy: four decades of experience. **J. Am. Coll. Cardiol**. 1989;14(7):1595-1608
22. BAKRIS GL, Jones J, Lass N, Gaber O, Burnett JC, Jr.: Radiocontrast medium-induced declines in renal functions: A role for oxygen free radicals. **Am. J. Physiol**1990;258 (Renal Fluid Electrolyte):F115-F120.
23. BAKRIS GL, Gaber DA, Jones JD: Oxygen free radical involvement in urinary Tamm- Horsfall protein excretion after intrarenal injection of contrast medium. **Radiology** 1990;175:57-60.
24. Sauter E, BAKRIS GL: The effects of enalapril on urinary protein excretion in patients with idopathic membranous nephropathy. **J. Clin Pharmacol** 1990; 30:155-158.
25. BAKRIS GL: The comparative effects of diltiazem and lisinopril on urinary protein excretion in diabetic patients. **Ann Intern Med** 1990;112(9):707-708.
26. Porile JL, BAKRIS GL, Garella S: Acute interstitial nephritis with glomerulopathy due to nonsteroidal anti-inflammatory agents: A review of its clinical spectrum and effects of steroid therapy. **J. Clinical Pharmacology** 1990;30:468-475.
27. BAKRIS GL, Sauter ER, Hussey J, Fischer J, Gaber AO, Winsett R: Effects of theophylline on erythropoietin production in normal subjects and in patients with erythrocytosis after renal transplantation. **N Engl. J. Med**. 1990;323:86-90.

28. BAKRIS GL and Frohlich ED: Calcium antagonists: new indications. **Curr. Opinion in Cardiol**.1990;5(5):630-634.

29. Demarie B, BAKRIS GL: Effects of different calcium antagonists on proteinuria associated with diabetes mellitus. Annals of Internal Med. 1990; 113(12):987-988.

30. Karp S, BAKRIS GL, Rubenstein D, Hou S: Tobramycin induced exfolative dermatitis in a peritoneal dialysis patient. A case report and literature review. **Cutis** 1991;18:167-168.

31. BAKRIS GL, Fairbanks RF, Traish A, with technical assistance by Akerstrom V, and Kern S: Arginine vasopressin stimulates human mesangial cell production of endothelin. **J. Clin Investigation**, 1991;87:1158-1164

32. Valentino V, Wilson M, Weart W, and BAKRIS GL: Effects of calcium antagonists and angiotensin converting enzyme inhibitors on diabetic nephropathy: **Arch Intern Med**. 1991;151:2367-2374.

33. BAKRIS GL and Gavras H: Hypertension in the Elderly: An editorial review. **Geriatric Nephrol and Urology**, 1991;1:121-127.

34. BAKRIS GL. Renal effects of calcium antagonists in diabetes mellitus: An overview of studies in animal models and in humans. **Am. J. Hypertens** 1991;4(Suppl II):487S-493S.

35. BAKRIS GL. The effects of calcium antagonists on renal hemodynamics, urinary protein excretion and glomerular morphology in diabetic states. **J. Am. Soc. Nephrology** 1991; 2 (Suppl 1):S21-S29.

36. Valentino V and BAKRIS GL: Clinical management of isolated systolic hypertension. **Practical Cardiology** 1991;17(6):26-30.

37. Weir MR and BAKRIS GL: Risk for renal injury in diabetic hypertensive patients. **Postgraduate Med**. 1992;91(3):77-95

38. BAKRIS GL, Barnhill BW, Sadler R: Treatment of arterial hypertension in diabetic man: Importance of therapeutic selection. **Kidney International**, 1992;41(4): 912-919.

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ABSTRACTS (over 290-not listed)

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BOOK EDITOR

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Sobel B and BAKRIS GL. **Hypertension: A Clinician's Guide to Diagnosis and Treatment.** Sobel and Bakris (eds.) Hanley and Belfus, Philadelphia, 2nd ed. 1999

Book Editor (Cont.)

BAKRIS GL. **The Kidney and Hypertension** Dunitz Publishing, London, 2003
Lip GYH and BAKRIS G **Handbook of Hypertension**, Science Press, NJ, 2005
Caralis D and BAKRIS GL. **Lower Extremity Arterial Disease**, Humana Press, 2005
Battguay, E, Lip G and BAKRIS, GL. **Comprehensive Hypertension**, Elsevier Press, 2006
BAKRIS, GL. **The Kidney in Cardiovascular Disease**, Dunitz Publishing, 2006
BAKRIS GL. **Therapeutic Strategies in Hypertension.** Clinical Pub. Oxford, UK, 2006
Bell DSH, O'Keefe JH, and BAKRIS GL (Eds.) **Handbook of Diabetic Hypertension** Physicians' Press, Royal Oak, MI, 2006
BAKRIS, GL. **Contemporary Diagnosis and Management of Hypertension and Diabetes**. Handbooks in Health Care Co. Newtown, PA, 2007
BAKRIS, GL **Microalbuminuria: Marker of Kidney and Cardiovascular Disease** Current Medicine Group, London, 2007
BAKRIS, GL **Cardiovascular Risk and the Kidney**, Dunitz Publishing, 2007-In preparation

ASSOCIATE Book Editor-

International Textbook of Cardiology Crawford MH, DiMarco JP and Paulus WJ (eds), 2004 and 2006 editions
Current Diagnosis & Treatment in Nephrology- The Lange Series, Nissensen A, Berns JS and Lerma E (Eds.) 2008 McGraw-Hill Pub., New York

Visiting Professorships

University of Hawaii, Nephrology Group-Honolulu, HI- July, 1992.
U. of So. Cal./LA County Hospital, Endocrine/Nephrology Sections-August, 1992
U of Miami School of Medicine, Nephrology section, Miami, FL., Jan.1994
Brookdale Medical Center, Nephrology section, Brooklyn, NY, October,1994
Royal University of Liverpool, Endocrinology Dept. -Liverpool, UK, Oct. 1994
U of Leicester, Hypertension/Medicine Dept- Leicester, UK, October, 1994
Guy's Hospital, Endocrinology Dept.- London, UK, June, 1995
Ohio State U Med. Center, Nephrology section-Columbus, Ohio, Mar, 1996
Allegheny University Med. Center, Nephrology-Philadelphia, PA, Nov, 1996
The Diabetes Institutes-Eastern Virginia Med School, Norfolk, VA, April, 1997
University of Washington, Nephrology Section, Seattle, WA, November, 1997
Ohio State University, Nephrology Section, Columbus, Ohio, February, 1998
U of Melbourne, Royal Melbourne Hosp, Melbourne, Australia, Mar. 1998
University of Maryland, Baltimore, MD, April, 1998
Joslin Diabetes Center, Boston, MA, October, 1999
Columbia University Medical Center, New York, NY April, 2000
University of Athens School of Medicine, Athens, Greece, September, 2000
Visiting Professorships (cont.)
King Fisal University Medical School, Riyadeh, Saudi Arabia, January, 2001
Yale/New Haven Medical Center-New Haven, Conn., January, 2002

University of Florida, Gainsville, FL-April, 2003
Columbia Presbyterian/Cornell Hospitals, New York, May, 2003
Joslin Diabetes Center, January, 2004
Ottawa Heart Institute, Ottawa Canada, May, 2004
U of Washington, Seattle-Sept, 2004
U of Wisconsin, Madison-Nov., 2004
U of Alabama, Birmingham-Dec., 2004
U of Hawaii, Honolulu-Jan, 2005
U of California Los Angeles (UCLA)-Jan, 2005
Oxford University-Oxford, UK-Sept. 2005
East Virginia University, Norfolk, VA-Sept-2005
Kimmelstiel Lecturer (visiting professor)-U of Melbourne, Australia-July, 2006

INVITED LECTURES AND WORKSHOPS (summarized):

National and International Meetings & Symposia: Approximately 650 since 1985

Serial No. 09/892,505
Atty. Doc. No. 11160-002

EXHIBIT C: SECOND DECLARATION OF RICHARD J. JOHNSON, M.D. 4 pages

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner	:	Kantamneni, Shobha
Art Unit	:	1617
Applicants	:	Kivlighn et al.
Serial No.	:	09/892,505
Filed	:	June 28, 2001
For	:	Treatment For Cardiovascular Disease

SECOND DECLARATION OF RICHARD JOHNSON, M.D.

I, Richard Johnson. hereby declare and say as follows:

THAT, I am employed as a Professor of Medicine at the University of Florida, Gainesville, FL.;

THAT, I am one of the above-named Applicants and inventors of the subject matter described and claimed in the above-identified patent application;

THAT, by virtue of my educational and employment background, my attendance at seminars, my ongoing research, my continuing review of scientific periodicals and journals, and through correspondence with professional colleagues, I am aware of the level of skill of one ordinarily skilled in the art of cardiovascular disease and kidney disease, and in particular, mechanisms of hypertension;

THAT, I have studied the application Serial No. 09/892,505 and office actions which have been issued during prosecution of this application (including cited references), as well as responses which have been filed on the Applicants' behalf, and being thus duly qualified declare as follows:

1. I have studied the Nakamoto European patent (Nakamoto Patent) cited by the Examiner in the subject application. The Nakamoto patent is directed to a new uricosuric compound; not to a xanthine oxidase inhibitor. However, the Nakamoto patent makes one statement that the U.S. Patent Office relies on for its allegation that Nakamoto discloses that compounds which reduce uric acid are effective in curing hypertension[1]. Nakamoto reasons that if gout is associated with hypertension, then curing gout with its uricosuric compound will cure hypertension (page 7, lines 55). This reasoning in the

Nakamoto reference is so defective from a medical/scientific perspective that even a person with little skill in the art would immediately reject it. Those trained in science and medicine are careful not to confuse association with causation. The Nakamoto patent authors clearly make this mistake. As an example, let's assume that a study finds that smoking is associated with liver cirrhosis. Those skilled in the art would not conclude from this that smoking causes liver cirrhosis (rather the medical community would undoubtedly interpret this study to mean that many people who smoke also drink). The only way to determine whether smoking causes liver cirrhosis or to determine whether uric acid causes hypertension is to test the hypothesis by conducting a scientific study. I note that Nakamoto provides zero supporting data or evidence to support its reasoning.

2. To my knowledge, there have never been any clinical trials using the Nakamoto uricosuric compound. Had those skilled in the art thought that the Nakamoto uricosuric compound could cure or prevent hypertension by lowering uric acid, certainly there would have been studies to test the compound for this purpose or studies testing other known uricosurics. However, the scientific and patent literature reveals that the Nakamoto patent was not accepted as presenting a cure for hypertension, whether by administering its uricosuric compound or otherwise. A literature search in the PubMed database and a patent search of the USPTO database using the authors' names (and U.S. Counterpart 4,883,821) identified no citations to their work. In contrast, members of the famous Framingham Heart Study group, experts in the field of hypertension, declared in 1999 (note that the Nakamoto patent was issued in 1991) that uric acid does not play a causative role in hypertension[2], such conclusion being supported by a comprehensive scientific study.

3. The undersigned declares further that all statements made herein of his own knowledge are true and that all statements made on information in belief are believed to be true; and further that these statements were made with the knowledge that willful false statements in the like so made are punishable by fine or imprisonment, or both, under §1001 of title 18 of the U.S.C. and that such willful false statements made jeopardize the validity of the application or of any patent issuing thereon.

Further declarant sayeth naught.

Richard J Johnson, M.D.
Professor and Chief,
Division of Nephrology, Hypertension and Transplantation
University of Florida
Oct 27th, 2007

1. The Nakamoto patent states that its diuretic compound "is effective in curing gout by ameliorating and curing hyperuricemia. This disease often accompanies hypertension, arteriosclerosis and myocardial infarction because of characteristics of the disease. Accordingly, the compound of the present invention is effective in curing or preventing hypertension, arteriosclerosis or myocardial infarction accompanied by hyperuricemia." (page 7, line 55-59)

2. Culleton BF, Larson MG, Kannel WB, Levy D. Serum uric acid and risk for cardiovascular disease and death: the Framingham Heart Study. *Ann Intern Med* 1999;131:7-13.

Serial No. 09/892,505

Atty. Doc. No. 11160-002

EXHIBIT D: DECLARATION OF MATTHEW R WEIR, M.D. 4 pages.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner	:	Kantamneni, Shobha
Art Unit	:	1617
Applicants	:	Kivlighn et al.
Serial No.	:	09/892,505
Filed	:	June 28, 2001
For	:	Treatment For Cardiovascular Disease

DECLARATION OF MATTHEW R WEIR, M.D.

I, Matt Weir, M.D., hereby declare and say as follows:

THAT, I am Professor and Director of the Division of Nephrology at the University of Maryland School of Medicine. I am a world expert in the field of hypertension and have published over 300 papers. I am well versed with the work of Dr Johnson, particularly as it relates to his work with uric acid.

THAT, I am aware of the level of skill of one ordinarily skilled in the art of cardiovascular disease and kidney disease, and in particular, mechanisms of hypertension, hereto; AND being thus duly qualified declare as follows:

1. I have read the Nakamoto European patent (Nakamoto Patent) cited by the Examiner in the subject application. The Nakamoto patent is directed to a new uricosuric compound; not to a xanthine oxidase inhibitor. Importantly, the Nakamoto patent makes a curious statement, which the U.S. Patent Office relies on for its allegation that Nakamoto discloses that compounds which reduce uric acid are effective in curing hypertension[1]. Nakamoto reasons that if gout is associated with hypertension, then curing gout with its uricosuric compound will cure hypertension (page 7, last line). In fact, it has been known for over 40 years that uric acid is strongly associated with hypertension[2]. Nevertheless, those skilled in the art of science and medicine are careful to not confuse something considered as an associative factor with something that is a causative factor. Nakamoto made the classic mistake of equating association with causation. As an example, let's assume that a study finds that drinking alcohol is associated with lung cancer. Those skilled in the art would not assume from this that

drinking alcohol causes lung cancer (rather the medical community would undoubtedly interpret this study to mean that many people who drink also smoke). The only way to determine whether abstaining from alcohol causes lung cancer or to determine whether uric acid causes hypertension is to test the hypothesis by conducting a scientific study.

While the association of uric acid with hypertension has been known since our early work, this certainly did not prove that uric acid is a cause of hypertension. Indeed, the scientific community (as exemplified by guidelines published by the major societies on hypertension and cardiovascular disease) have not considered uric acid as having a causal role in hypertension. In this regard, Dr Johnson is the first to specifically investigate if uric acid might be a cause of hypertension and to provide direct evidence of such. As such, the Nakamoto reference is flawed from a medical/scientific perspective that even a person with little skill in the art would discount it outright, especially since Nakamoto provides zero supporting data or evidence that uric acid is a cause of hypertension. Consistent with this point, a literature search in the PubMed and patent search of the USPTO database using the authors' names (and U.S. Counterpart 4,883,821) identified no citations to their work.

2. Members of the famous Framingham Heart Study group, experts in the field of hypertension, declared in 1999 (note that the Nakamoto patent was issued in 1991) that uric acid does not play a causative role in hypertension[3], such conclusion being supported by a comprehensive scientific study. Indeed, as of 2000, the scientific evidence, supported by actual research and data, lead those skilled in the art to believe that there is no reasonable expectation of successfully controlling hypertension by controlling a patient's uric acid levels. Said differently, the scientific, peer-reviewed literature taught away from controlling uric acid levels to control hypertension. Incidentally, in 2005, members of the Framingham Heart Study Group reversed their position and published an acknowledgement that serum uric acid plays a causative role in hypertension[4], citing to Dr. Johnson's work[5].

3. The undersigned declares further that all statements made herein of his own knowledge are true and that all statements made on information in belief are believed to

be true; and further that these statements were made with the knowledge that willful false statements in the like so made are punishable by fine or imprisonment, or both, under ' 1001 of title 18 of the U.S.C. and that such willful false statements made jeopardize the validity of the application or of any patent issuing thereon.

Further declarant sayeth naught.

[name]

12/3/07
Date

1. The Nakamoto patent states that its diuretic compound "is effective in curing gout by ameliorating and curing hyperuricemia. This disease often accompanies hypertension, arteriosclerosis and myocardial infarction because of characteristics of the disease. Accordingly, the compound of the present invention is effective in curing or preventing hypertension, arteriosclerosis or myocardial infarction accompanied by hyperuricemia." (page 7, last line)

2. Cannon PJ, Stason WB, Demartini FE, Sommers SC, Laragh JH. Hyperuricemia in primary and renal hypertension. *N Engl J Med* 1966;275:457-64.

3. Culleton BF, Larson MG, Kannel WB, Levy D. Serum uric acid and risk for cardiovascular disease and death: the Framingham Heart Study. *Ann Intern Med* 1999;131:7-13.

4. Sundstrom, J., L. Sullivan, R.B. D'Agostino, D. Levy, W.B. Kannel, and R.S. Vasan, *Relations of serum uric acid to longitudinal blood pressure tracking and hypertension incidence,* Hypertension, 2005 45(1): p. 28-33)

5. Mazzali M, Hughes J, Kim YG, Jefferson JA, Kang DH, Gordon KL, Lan HY, Kivlighn S, Johnson RJ. Elevated uric acid increases blood pressure in the rat by a novel crystal-independent mechanism. *Hypertension* 2001;38:1101-6.

RELATED PROCEEDINGS APPENDIX

None.